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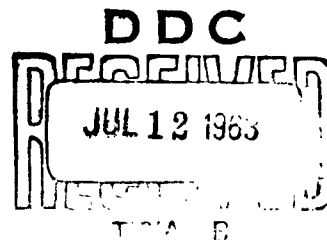
INHIBITION OF URETHAN LUNG TUMOR INDUCTION IN
MICE BY TOTAL-BODY X IRRADIATION

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by
W. A. Foley
L. J. Cole

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U.S. NAVAL RADIOLOGICAL
DEFENSE LABORATORY
SAN FRANCISCO 24, CALIFORNIA

EXPERIMENTAL PATHOLOGY BRANCH

L. J. Cole, Head

BIOLOGICAL AND MEDICAL SCIENCES DIVISION

E. L. Alpen, Head

ADMINISTRATIVE INFORMATION

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Eugene P. Cooper

Eugene P. Cooper
Scientific Director

E. B. Roth

E. B. Roth, CAPT USN
Commanding Officer and Director

ABSTRACT

Groups of young adult (C57L x A) F_1 mice received a single intraperitoneal injection of urethan prior to or after a single whole body lethal dose of X rays (880 rad) followed by transfusion of normal syngeneic bone marrow to protect against radiation death. This dose of urethan produced multiple tumors in 100% of nonirradiated animals at 24 weeks postinjection. In the irradiated animals there was marked suppression of lung tumor formation, both in number of animals with tumors, and in numbers of tumors per tumor-bearing animal. This suppression was present whether urethan treatment preceded or followed radiation. The results imply that urethan lung carcinogenesis may be interfered with by a direct inhibitory effect of the radiation on cells already altered by urethan, or through latent radiation inhibition of pulmonary alveolar proliferative capacity.

SUMMARY

The Problem:

Administration of the compound, urethan, to certain strains of mice is known to elicit lung tumors in high frequency. Earlier observations showed that mice restored by marrow injection following otherwise lethal doses of X radiation, showed fewer lung tumors than did nonirradiated controls. It was of interest, therefore, to inquire whether similar exposure of mice to high doses of X radiation would suppress the formation of urethan-induced lung tumors.

The Findings:

A single intraperitoneal injection of urethan (1 mg/g body weight) into young adult LAF₁ mice produced multiple lung tumors (mean of 5.6 tumors per mouse) in 100% of the mice sacrificed 24 weeks after injection. When urethan-injected mice received a single whole-body exposure to a lethal dose of X rays (880 rad), followed by isogenic bone marrow transfusion to protect against radiation death, the percentage of mice with pulmonary tumors, and the number of tumors per mouse were sharply reduced. A definite and marked reduction in urethan pulmonary tumor incidence was also observed when the X radiation was given prior to urethan injections. These findings imply that urethan-lung carcino-

genesis may be modified by a direct inhibitory effect of a high dose of X rays on lung cells already altered by urethan, or through latent radiation suppression of alveolar cell proliferative capacity.

INTRODUCTION

The compound, urethan (ethyl carbamate) is a potent carcinogen capable of producing pulmonary tumors in 100% of susceptible animals after a single injection (14, 19). Interest in urethan in our Laboratory followed reports of its effects on bone marrow (18), and experimental evidence of its ability to provide increased radioresistance in mice to X irradiation has been published (6). In the course of these and other experiments the question of radiation sensitivity of urethan tumor induction arose. Observations from several different experiments and certain theoretical considerations, led us to suspect that X irradiation might inhibit urethan pulmonary tumor induction. The experiments reported here show a marked suppression of pulmonary tumor formation when total body X-irradiation (880 rad) was carried out either before or after a single intraperitoneal injection of urethan, which by itself evoked multiple tumors in 100% of nonirradiated control animals.

MATERIALS AND METHODS

Ninety five LAF₁ male mice aged 9-10 weeks (18 - 21 grams) at the time of urethan injection were employed in these experiments. They were housed 7 to 10 per cage in galvanized metal cages with free access to tap water and Purina laboratory chow.

The animals were randomly divided into the following experimental groups: 1) untreated controls; 2) radiation only controls; 3) urethan only controls; 4) urethan followed 1 week later by radiation; 5) urethan

followed 24 hours later by radiation; 6) urethan followed 3 hours later by radiation; 7) radiation followed 3 hours later by urethan.

X irradiation was carried out in a single whole-body exposure of mice in individual, perforated lusteroid tubes on a circular wooden turntable rotating at 3.5 rpm. The dose was 880 rad. The radiation factors were: 250 kvp, 15 ma; filter 0.5 mm Cu plus 1.0 mm Al; HVL, 1.28 mm Cu; 100 cm target to skin distance; dose rate, 30 rad/min. Twenty four hours after this exposure, the irradiated mice received by iv injection approximately 6×10^6 marrow cells from syngeneic (i.e., LAF₁) donors aged 6 - 8 weeks, in order to protect against acute radiation death (5).

All animals were observed until the time of sacrifice, 24 weeks following urethan treatment; and to the same age for the nonurethan controls. They were sacrificed by cervical dislocation, and an immediate gross autopsy done. The extirpated lungs and trachea were fixed intact in Telleyesniczky acetic alcohol formalin (11) for 24 hours. At that time, careful counts of gross pulmonary tumors on the surfaces of the lungs were made, and the tissues were prepared for microscopic examination.

RESULTS

Pulmonary Tumors: The findings on percent of mice with tumors, and number of tumors per mouse are presented in Table I. None of the untreated controls, and only one of the 10 X-ray control mice had a

TABLE I
RADIATION INHIBITION OF
URETHAN PULMONARY TUMOR INDUCTION IN MICE*

TREATMENT	NUMBER OF MICE in group	NUMBER OF MICE with tumors	NUMBER OF TUMORS total	NUMBER OF TUMORS per mouse (mean) **
None	9	0	0	0
X ray only	10	1	1	1
Urethan only	16	16	89	5.6
Urethan, X ray 1 week later	15	8	12	1.5
Urethan, X ray 24 hours later	15	2	2	1.0
Urethan, X ray 3 hrs later	15	2	2	1.0
X ray, Urethan 3 hrs later	15	3	4	1.3

* Male IAF₁, treated at 9 - 10 weeks of age, sacrificed 24 weeks later.

** in tumor-bearing mice.

† X ray 5 880 rad whole body X irradiation followed 24 hrs later by
6 x 10⁶ syngeneic marrow cells i.v.

Urethan - ethyl carbamate (U.S.P.) 1 mg/g body weight

pulmonary tumor at the time of sacrifice. Treatment with urethan alone produced multiple tumors (mean of 5.6 per mouse) in 100% of the animals. By contrast, exposure of the urethan-treated mice to 880 rad of X rays sharply reduced the number of mice with pulmonary tumors, when the radiation was administered either 24 hours after, 3 hours after, or 3 hours before the single injection of urethan, i.e., as few as 2 mice with tumors out of 15, versus 16 mice with tumors out of 16. Furthermore, the total number of pulmonary tumors observed was markedly decreased from 89 in the urethan only group to 2 in the groups of mice which received urethan plus radiation 3 hours later or 24 hours later. When the radiation treatment followed urethan by one week, the number of tumor-bearing animals was about half that of the control, urethan only, group, and the average number of tumors per tumor bearing mouse was also reduced (1.5 versus 5.6 tumors per mouse). It is of interest that a definite and marked reduction in urethan pulmonary tumor incidence was also observed when the X radiation was given 3 hours prior to urethan.

Histopathology

All gross pulmonary tumors were confirmed by microscopic examination (Figure 1). They were similar in description to that given by others for spontaneous and urethan-induced neoplasms in the mouse lung (4,20). Both compact and adenoid patterns were observed, sometimes in the same gross lesion, and no difference in histology of the pulmonary tumors could be detected between the irradiated and nonirradiated tumor-bearing

animals. Although no evidence of metastasis was found in these experiments, we have seen extension of such tumors to regional lymph nodes in other experiments in which urethan-treated mice were allowed to live for periods of one year or more after treatment. In addition, seven animals from the present series showed focal areas of "adenomatous" change (Figures 2 and 3) which was morphologically distinct from the tumors, in that they were flush or retracted from the lung surface (in contrast to the bulging of tumors), and on microscopic examination showed areas of alveolar cell proliferation, inflammatory cellular infiltrate, fibrous thickening of alveolar walls, and cellular debris in the alveolar lumina. Two of these mice were in the urethan only group, two in the group given radiation 3 hours after urethan, and one each in the irradiated controls, untreated controls, and in the mice irradiated 24 hours after urethan.

No significant degree of glomerulosclerosis was observed in any of the animals. No cases of leukemia were seen in any of the groups, although microscopic examination of marrow and lymphoid organs was made in all cases. The liver showed no pathology on microscopic examination.

Body Weights

Data on body weights of the animals at the time of sacrifice are given in Table II. Significant differences ($p < 0.05$ by Student "t" test) in average body weight at time of sacrifice were observed between each group treated with the combination of urethan and radiation

Fig. 1 Pulmonary alveolar tumors in urethan treated mouse. Adenoid pattern in tumor on right and compact pattern in tumor on left. Note bulging of pleural surface in latter. H & E, 60X.

Fig. 2 An "adenomatous" lesion from a mouse radiated one week after urethan treatment. H & E, 125X.

Fig. 3 Higher magnification of Figure 2. Note proliferation of alveolar cells, and inflammatory reaction. H & E, 250X.

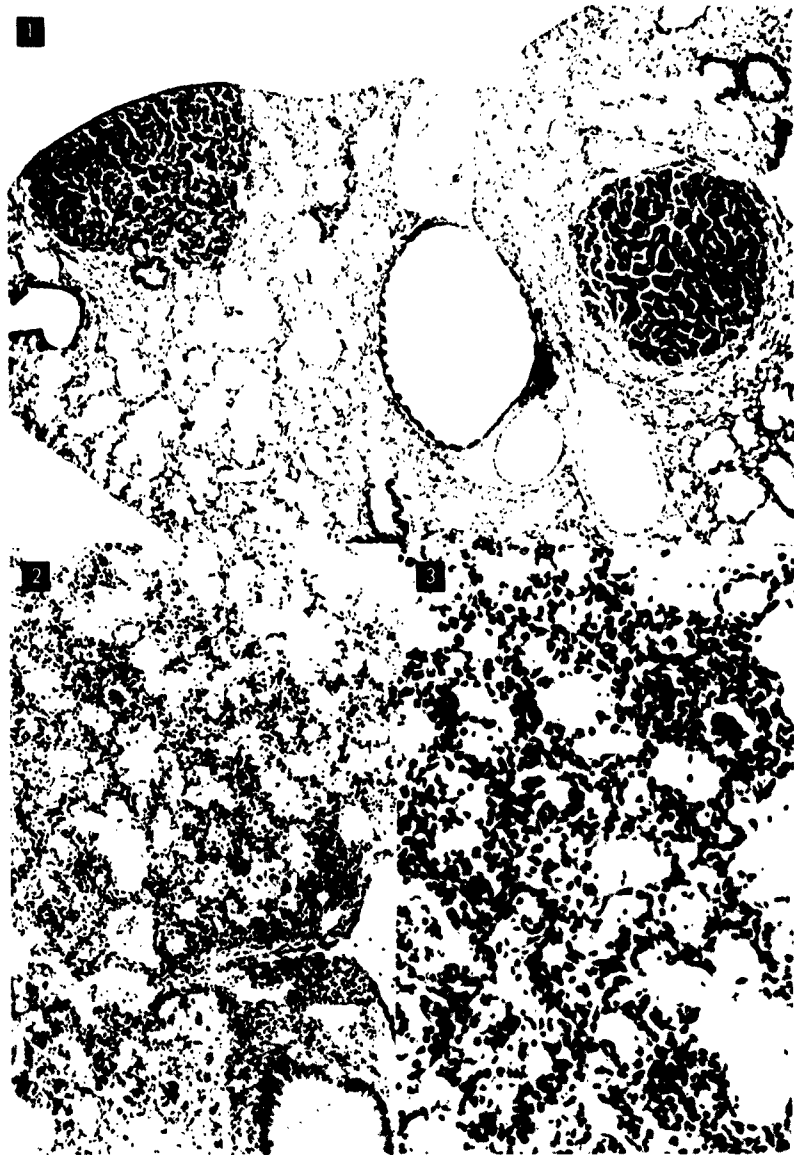


TABLE II

BODY WEIGHT OF URETHAN TREATED AND X-IRRADIATED MICE
AT TIME OF SACRIFICE*

TREATMENT	BODY WEIGHT(g)		% MICE WITH TUMORS
	<u>Mean \pm S.E.</u>	<u>Range</u>	
None	33.0 \pm 0.6	30.3 - 37.5	0
X ray only	29.8 \pm 0.8	26.0 - 34.9	10
Urethan only	34.0 \pm 0.9	31.4 - 42.5	100
Urethan, X ray 1 week later	27.9 \pm 0.5	24.8 - 41.0	53
Urethan, X ray 1 day later	27.5 \pm 0.4	25.1 - 30.1	13
Urethan, X ray 3 hrs later	27.2 \pm 0.4	24.9 - 30.8	13
X ray, Urethan 3 hrs later	28.1 \pm 0.5	24.1 - 31.2	20

* All mice weighed between 18 and 21 grams at time of random selection into groups for treatment. No significant differences in body weight were found between tumor bearing and non-tumor bearing mice in the individual groups.

versus each of the control groups (untreated, urethan only, radiation only), except that the group irradiated before urethan treatment did not differ from the radiation control group. The radiation control group also differed significantly from the untreated and from the urethan only groups.

DISCUSSION

A decreased incidence of pulmonary tumors in mice following large single doses of fast neutrons or X rays has previously been reported from this Laboratory (15) and by others (23) following gamma or neutron radiation. A similar reduction in nitrogen mustard-induced pulmonary tumors after X irradiation has been reported by Heston, et al. (8). The present data support the above findings of a radiation inhibition of alveolar cell proliferation, in this case induced by urethan. They also provide evidence for a latent radiation effect to the alveolar cells, in that mice treated with urethan 3 hours after X irradiation showed decrease in tumor incidence similar to that seen in those treated with urethan before X irradiation. This "latent" radiation inhibition is probably analogous to that previously reported from this Laboratory with respect to proliferative capacity of kidney (7), another tissue whose normal cell turnover rate, like lung, is relatively low. Furthermore, we have not found any histologic evidence of either urethan or X-ray effects on mouse lung in routine preparations studied over an acute (2 week) period following treatment. This observation confirms

previous reports in radiation (16) and urethan (13) experiments, and emphasizes the subcellular site of action of these agents. Urethan is presumed to exert its biological effect through interference with DNA synthesis, possibly at the level of the pyrimidine nucleotides (17). It is also known to be rapidly excreted from the animal body (2,3).

It is probable, on the basis of the above considerations, that this inhibitory effect of X radiation on urethan lung-tumorigenesis is critically dependent on the high radiation dose used. Therefore, at some lower dose level, or with fractionated X radiation (12) the lung carcinogenic effect of radiation may turn out to be additive with that of urethan. Experiments designed to resolve this point are in progress.

The "adenomatous" change seen in a few mice in several of the treatment and control groups is similar to that described by Horn, et al. (9). This lesion bears a microscopical resemblance to the contagious alveolar proliferation (jaagsiekte) in sheep. Similar lesions have been described in man (1). A recent report (22) on such lesions in DBA mice following urethan treatment, interpreted them as a neoplastic response. The specific etiology of this lesion is not known, and the multiplicity of names that have been applied to it bears witness to the lack of agreement which surrounds it. Its occurrence in this study was too infrequent and sporadic to allow any definite conclusions, but we feel with Horn, et al. (9) that this "adenomatous" change is an inflammatory response, and not a true neoplasm.

The mechanism by which a single, high dose of whole body X radiation antagonizes the lung-carcinogenic effect of urethan is not known. At first sight this effect seems perhaps paradoxical, since urethan is itself radiomimetic. We have considered two possible hypotheses: 1) that the radiation produces intracellular damage such that the capacity for proliferation on the part of the alveolar cells is inhibited (at least for a time), and therefore that the population of cells able to emerge as tumors due to the carcinogenic or co-carcinogenic effect of urethan is greatly reduced; 2) that the interaction of urethan with a biochemical "target" (possibly DNA) involved in the carcinogenic change, is somehow interfered with under conditions in which X radiation is applied shortly before (3 hours) or shortly after (3 or 24 hours) urethan. Perhaps there is competition between X radiation and urethan for the same 'target' site. It is noteworthy to point out in support of this concept that the suppressive effect of X radiation on urethan lung-tumorigenesis was appreciably lessened when the radiation was given 1 week after urethan, as compared with 1 day or 3 hours after urethan (Table I). Apparently some urethan-induced changes, related to eventual carcinogenesis, already had occurred in the lung cells within one week after urethan injection.

There remains the possibility that the time of sacrifice in these experiments (24 weeks posttreatment) does not measure the true carcinogenicity of urethan plus radiation; if these animals were allowed to live for a larger fraction of their life span, more tumors might arise

in the irradiated animals. However, it is probable that more tumors per animal also would be found in the animals treated with urethane only (19).

The question of body weight reduction, reflecting reduced caloric intake or urethan toxicity, as a possible factor in suppression of tumor formation must be considered in light of the body weight data (cf 21). The fact that a similar weight reduction failed to give similar tumor inhibition (i.e., in the group irradiated one week after urethan versus the other group), would seem to indicate that failure to gain weight was a concomitant and not a causal factor in pulmonary tumor inhibition. Furthermore, in the experiments of Larsen and Heston (10) decrements in body weight, similar to those observed here, were produced by caloric restriction, but did not elicit significant changes in spontaneous tumor incidence in male strain A mice; still more profound reduction in body weight (by caloric restriction) yielded a smaller reduction in spontaneous pulmonary tumor incidence than was seen in the present experiments.

Experiments are now in progress in the attempt to resolve some of the questions raised by the present findings, i.e., to determine the effect of fractionated X-radiation on urethan-induced lung tumorigenesis; to ascertain whether the radiation effect is direct or indirect through partial shielding; and to evaluate the role of proliferative capacity of alveolar cells, by means of autoradiography.

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